

Promising tools for future drug discovery and development in antiarrhythmic therapy

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Running Title: Visualizing Future Antiarrhythmics

Financial Support: This work was supported by National Institutes of Health R01 HL163943; La Caixa Banking Foundation [project code638LCF/PR/HR19/52160013]; grant PI20/01220 of the public call “Proyectos de Investigación en Salud 2020” [PI-FIS-2020] funded by Instituto de Salud Carlos III (ISCIII); MCIU grant BFU2016-75144-R and PID2020-116935RB-I00, and co-founded by Fondo Europeo de Desarrollo Regional (FEDER); and Fundación La Marató de TV3642 [736/C/2020]. We also receive support from the European Union's Horizon 2020 Research and Innovation programme [grant agreement GA-965286]. CNIC is supported by the Instituto de Salud Carlos III (ISCIII), the Ministerio de Ciencia e Innovación (MCIN) and the Pro CNIC Foundation, and is a Severo Ochoa Center of Excellence [grant CEX2020-001041-S649 funded by MICIN/AEI/10.13039/501100011033].

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32 **Keywords:** arrhythmias, drug discovery, novel antiarrhythmics therapy, ion channels, iPSC
33 technology, multi-omics, peptibodies, HTS

34

35 **Manuscript statistics**

36 Number of text pages: 91

37 Number of tables: 0

38 Number of figures: 1

39 Reference count: 272

40 Abstract word count: 242

41

42

43

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45

46 **Abstract**

47 Arrhythmia refers to irregularities in the rate and rhythm of the heart, with symptoms spanning
48 from mild palpitations to life-threatening arrhythmias and sudden cardiac death (SCD). The
49 complex molecular nature of arrhythmias complicates the selection of appropriate treatment.
50 Current therapies involve the use of antiarrhythmic drugs (class I-IV) with limited efficacy and
51 dangerous side effects and implantable pacemakers and cardioverter-defibrillators with
52 hardware-related complications and inappropriate shocks. The number of novel antiarrhythmic
53 drugs in the development pipeline has decreased substantially during the last decade and
54 underscores uncertainties regarding future developments in this field. Consequently, arrhythmia
55 treatment poses significant challenges, prompting the need for alternative approaches.
56 Remarkably, innovative drug discovery and development technologies show promise in helping
57 advance antiarrhythmic therapies. Here, we review unique characteristics and the transformative
58 potential of emerging technologies that offer unprecedented opportunities for transitioning from
59 traditional antiarrhythmics to next-generation therapies. We assess stem cell technology,
60 emphasizing the utility of innovative cell profiling using multi-omics, high-throughput screening,
61 and advanced computational modeling in developing treatments tailored precisely to individual
62 genetic and physiological profiles. We offer insights into gene therapy, peptide and peptibody
63 approaches for drug delivery. We finally discuss potential strengths and weaknesses of such
64 techniques in reducing adverse effects and enhancing overall treatment outcomes, leading to
65 more effective, specific, and safer therapies. Altogether, this comprehensive overview introduces
66 innovative avenues for personalized rhythm therapy, with particular emphasis on drug discovery,
67 aiming to advance the arrhythmia treatment landscape and the prevention of SCD.

68 **Significance Statement**

69 Arrhythmias and sudden cardiac death account for 15–20% of deaths worldwide. However,
70 current antiarrhythmic therapies are ineffective and with dangerous side effects. Here, we
71 review the field of arrhythmia treatment underscoring the slow progress in advancing the cardiac
72 rhythm therapy pipeline and the uncertainties regarding evolution of this field. We provide
73 information on how emerging technological and experimental tools can help accelerate progress
74 and address the limitations of antiarrhythmic drug discovery.

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89 **Abbreviations**

- 90 Acetylcholine activated inward rectifier potassium current (I_{KACh})
- 91 Antiarrhythmic drugs (AADs)
- 92 Action potential (AP)
- 93 Action potential duration (APD)
- 94 Andersen-Tawil Syndrome Type 1 (ATS1)
- 95 Antisense oligonucleotides (ASOs)
- 96 Artificial Intelligence (AI)
- 97 Atrial fibrillation (AF)
- 98 Atrioventricular node (AVN)
- 99 Calcium or calmodulin-dependent protein kinase II (CaMKII)
- 100 Catecholaminergic polymorphic ventricular tachycardia (CPVT)
- 101 Chromatin-immunoprecipitation sequencing (ChIP-seq)
- 102 Comprehensive in-vitro Proarrhythmia Assay (CiPA)
- 103 Delayed rectifier potassium current (I_{Kr})
- 104 Docohexaenoic acid (DHA)
- 105 DNA methylation sequencing (Methyl-seq)
- 106 Duchenne muscular dystrophy (DMD)
- 107 Engineering heart tissues (EHTs)
- 108 Extracellular matrix (ECM)
- 109 Field potential duration (FPD)
- 110 Fragment crystallizable (Fc)
- 111 Heart rate (HR)

- 112 High-Throughput Screening (HTS)
- 113 Human ether-a-go-go-related gene (hERG)
- 114 Human induced Pluripotent Stem Cell (hiPSC)
- 115 hiPSC-derived cardiomyocytes (hiPSC-CMs)
- 116 Immunoglobulin G (IgG)
- 117 Implantable cardioverter-defibrillators (ICDs)
- 118 Inherited retinal disease (IRD)
- 119 Insulin-like growth factor-1 (IGF-1)
- 120 Inward rectifying potassium current (I_{KI})
- 121 Lipoprotein lipase deficiency (LPLD)
- 122 Liquid chromatography and mass spectrometry (LC-MS)
- 123 Locked nucleic acid (LNA) antimiRs
- 124 Long noncoding-RNAs (lncRNAs)
- 125 Long QT syndrome (LQTS)
- 126 Mass spectrometry (MS)
- 127 Microelectrode array (MEA)
- 128 Myocardial Infarction (MI)
- 129 Next-generation sequencing (NGS)
- 130 Non-Invasive electrocardiographic imaging (ECGI)
- 131 Organ-on-a-chip (OoC)
- 132 Paroxysmal supraventricular tachycardia (PSVT)
- 133 Platelet-derived growth factor (PDGF)
- 134 Postoperative atrial fibrillation (POAF)

- 135 Quantitative Structure-Activity Relationship (QSAR)
- 136 Recombinant adeno-associated viruses (rAAVs)
- 137 RNA interference (RNAi)
- 138 RNA-sequencing (RNA-seq)
- 139 Ryanodine receptor 2 (RyR₂),
- 140 Serum Glucocorticoid inducible Kinase 1 (SGK-1)
- 141 SNPs (single-nucleotide polymorphisms)
- 142 Sodium current (I_{Na})
- 143 Spinal muscular atrophy (SMA)
- 144 STEM (science, technology, engineering and mathematics)
- 145 Sudden cardiac death (SCD)
- 146 TertiapinQ peptidotoxin (TP)
- 147 Torsade de Pointes (TdP)
- 148 Transcription activator-like effector nucleases (TALENs)
- 149 Tyrosine kinase inhibitors (TKI)
- 150 Variants of uncertain significance (VUSs)
- 151 Zinc-finger nucleases (ZFN)

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176 **1. Introduction**

177 Cardiac arrhythmias are abnormal heart rhythms that can lead to serious health problems,
178 including heart failure and sudden cardiac death. Current antiarrhythmic treatments are empirical
179 and subject to clinical judgment. They remain a weakness in contemporary cardiovascular
180 medicine (Kingma et al., 2023; Schwartz et al., 2020). A broad pharmacological arsenal designed
181 to modulate cardiac electrical activity exists aiming to restore the rhythm (Kingma et al., 2023).
182 However, the complex nature of arrhythmias, coupled with limited effectiveness plus side effects
183 associated with current therapeutic approaches, underscores the need for innovative strategies to
184 propel the field forward. Fortunately, several emerging technologies are showing promise in the
185 field of drug discovery and the development of antiarrhythmic therapies. Such technologies offer
186 unprecedented opportunities to revolutionize drug discovery and development, marking the onset
187 of a paradigm shift in the search for novel antiarrhythmic therapies. Transition from traditional
188 antiarrhythmics to next-generation therapies may boost precision medicine, with treatments
189 tailored to individual genetic, physiological and environmental profiles. Here, we explore for
190 potential antiarrhythmic drug discovery and development tools by first delving briefly into the
191 current landscape of antiarrhythmic therapy, critically evaluating the strengths and limitations of
192 existing pharmaceutical agents (Saljic et al., 2023; Valderrábano, 2022). Subsequent sections
193 describe the transformative potential of stem cell technology, multi-omics, advanced
194 computational modeling, and high-throughput screening, all of which are gaining attention in
195 drug discovery and development. We also look at the future potential of gene and peptide-based
196 therapies in treating cardiac arrhythmias. Together with an ever-increasing understanding of the
197 molecular mechanisms underlying cardiac arrhythmias, these technologies support an optimistic
198 outlook toward improved pharmacological treatment opportunities for patients suffering from

199 cardiac arrhythmias. These auspicious tools also offer a better understanding of the intricacies of
200 cardiac electrophysiology. They should help researchers develop new, more specific, safe, and
201 effective therapies that are also tailored to the unique characteristics of each patient, promoting
202 personalized medicine (Piccini et al., 2022). Therefore, this review aims to navigate the
203 trajectories toward future alternatives in antiarrhythmic therapies, highlighting promises and
204 challenges associated with them.

205 **2. The traditional Landscape of Antiarrhythmic Drug Therapy.**

206 Traditional antiarrhythmic drugs (AADs), categorized by their electrophysiological effects, are
207 currently what is best for controlling the electrical activity of the heart and managing rhythm
208 disturbances. Selecting the appropriate antiarrhythmic therapy depends on the specific type of
209 arrhythmia, its underlying cause, and individual patient characteristics (Al-Khatib et al., 2018;
210 Michowitz et al., 2021). Sodium channel blockers, or Class I AADs (quinidine, procainamide,
211 disopyramide, lidocaine, flecainide, propafenone), inhibit sodium channels during
212 depolarization, slowing the rate of rise of the action potential (AP), thus reducing cell excitability
213 and conduction velocity (Lei et al., 2018). Class Ic AADs agents, such as flecainide and
214 propafenone, also exert their antiarrhythmic effects by targeting the ryanodine receptor 2
215 (RyR2), a critical calcium release channel in the heart (Hilliard et al., 2010; Kryshtal et al., 2021;
216 Salvage et al., 2022; Watanabe et al., 2009). This action helps stabilize calcium handling and
217 reduces the risk of arrhythmogenic events, making these drugs particularly effective in treating
218 certain types of arrhythmias where calcium dysregulation plays a role (Bergeman et al., 2023;
219 Kryshtal et al., 2021; Y. Li et al., 2022). β -adrenergic receptor blockers, or Class II AADs like
220 propranolol, metoprolol and atenolol, reduce sympathetic stimulation and decrease heart rate
221 (HR) and contractility (Wołowiec et al., 2022). Class III AADs are potassium channel blockers

222 (e.g., amiodarone, sotalol, dofetilide) that prolong the repolarization phase of the AP (Pannone et
223 al., 2021; Roden, 2016). Similar to Class II, calcium channel blockers (Class IV AADs),
224 including verapamil and diltiazem, decrease the HR and contractility by inhibiting the calcium
225 influx during AP depolarization (Koldenhof et al., 2023; Meyer et al., 2023). There are other
226 drugs not categorized within these 4 classes that exhibit antiarrhythmic actions. For example,
227 digoxin, traditionally used in the most common clinical arrhythmia, atrial fibrillation (AF),
228 increases the force of myocardial contraction and impairs conduction through the atrioventricular
229 node (AVN) (Ziff & Kotecha, 2016). Adenosine, used to treat supraventricular tachycardias, also
230 slows conduction through the AVN and interrupts reentry across accessory AVN pathways (Ziff
231 & Kotecha, 2016; Gupta et al., 2021). Ranolazine is used in certain cases of angina and has also
232 shown antiarrhythmic efficacy by inhibiting the late sodium current, reducing calcium overload
233 (Frommeyer et al., 2016; Rouhana et al., 2021; Shenasa et al., 2016). Vernakalant, a relatively
234 novel therapy for AF, also shows antiarrhythmics effects blocking multiple ion channels
235 (Frommeyer et al., 2016, 2017; Hall & Mitchell, 2019). While these drugs have undoubtedly
236 improved patient outcomes, their use must be carefully selected and monitored due to potential
237 proarrhythmia (i.e., inducing new arrhythmias), limited efficacy, and adverse side effects. When
238 pharmacologic therapy is not sufficient, non-pharmacological interventions such as catheter
239 ablation and implantable devices are commonly used in the management of certain arrhythmias.
240 Implantable cardioverter-defibrillators (ICDs) are implanted to detect and treat life-threatening
241 ventricular arrhythmias by delivering an electric shock to restore normal rhythm. The use of
242 pacemakers helps to coordinate contraction between the heart chambers (Arenal et al., 2022;
243 Elsokkari & Sapp, 2021; Gopinathannair et al., 2019). However, it is extremely important to note

244 that patients treated with AADs or non-pharmacological interventions are not exempt from SCD
245 risk (Mazzanti et al., 2020; Priori et al., 2015; Richards et al., 2015).

246 Importantly, the chronic use of Class I and Class II antiarrhythmic agents is associated with a
247 significant risk of pro-arrhythmic effects and increased mortality, particularly in patients with
248 underlying heart conditions (Freemantle et al., 1999; Zylla et al., 2024). The most notable
249 evidence comes from the Cardiac Arrhythmia Suppression Trial (CAST), which found that the
250 use of flecainide and encainide, class I antiarrhythmics, resulted in a higher mortality rate
251 compared to placebo in post-myocardial infarction (MI) patients. Specifically, the trial revealed
252 that these drugs could actually precipitate fatal arrhythmias, leading to the early termination of
253 the study due to safety concerns (Cardiac Arrhythmia Suppression Trial (CAST) Investigators,
254 1989). While the risks are lower for, β -adrenergic receptor blockers (class II antiarrhythmics),
255 they must still also be used judiciously, particularly in patients with severe cardiac dysfunction.

256 In some cases, especially at high doses or in patients with severe heart failure, β -blockers can
257 cause excessive bradycardia, hypotension, or heart block, potentially leading to adverse
258 outcomes, including an increased risk of arrhythmias (Dondo et al., 2017; Freemantle et al.,
259 1999; Waldo et al., 1996). Despite such risks, β -adrenergic receptor blockers are still widely used
260 because their overall benefit in reducing SCD and improving survival in heart failure and post-
261 MI patients, which often outweighs their risks (Yndigeñ et al., 2024). The above considerations
262 highlight the need for careful patient selection and monitoring under antiarrhythmic therapy.

263 **3. Antiarrhythmic Therapy Development Pipeline, the last 10 years**

264 It has been estimated that the average cost of a traditional drug discovery pipeline is 2.6 billion
265 USD, and a complete traditional workflow can take over 12 years (Mohs & Greig, 2017).
266 Unfortunately, the number of novel antiarrhythmic targets and agents in the development

267 pipeline has decreased substantially during the last few decades due to conceptual, regulatory
268 and financial considerations (Saljic et al., 2023). We have analyzed the AAD therapy
269 development over the last 10 years using data extracted from www.ClinicalTrials.gov (**Figure**
270 **1**). Alarming, the total number of interventional clinical trials encompassing preclinical, I, II,
271 III and IV phases for the treatment of arrhythmias is significantly lower than in other areas of
272 medicine. Specifically, only a total of 440 studies have been completed and/or are under
273 development in the last decade (**Figure 1A**). This is striking because sudden cardiac death (SCD)
274 and arrhythmia represent a major worldwide public health problem, accounting for 15–20 % of
275 all deaths (Srinivasan & Schilling, 2018). About half of those 440 studies are in phase IV or
276 pharmacovigilance stage looking for side effects caused over time after approval and marketing
277 (**Figure 1B**). Studies in early stages such as preclinical, I and II show much lower percentages
278 supporting the fact that there is limited innovation in the field of antiarrhythmic therapy. Within
279 the different types of interventions, it can be observed that drug development, without other
280 types of interventions, leads with about 74%, followed very far behind by device development
281 (7.95%). While other areas like biologic medicine and gene therapy are growing rapidly, here
282 they account for 1.14% and 0.45% respectively without combination with other types of
283 interventions (**Figure 1C**). We also analyzed clinical trials focusing exclusively on
284 pharmacological interventions (325 studies). As shown in **Figure 1D**, most of the studies
285 (33.53%) are dedicated to clinical research and development of anticoagulant or antiplatelet
286 therapy aiming to mitigate the risk of cerebrovascular accident (stroke), as frequently occurs in
287 patients with AF. In addition to these strategies, 7.69% of clinical trials aim to explore
288 improvements related to pharmacology during cardiac surgery, mainly to advance ablation
289 techniques, improve cardiac device implantation (pacemaker, defibrillator, cardiac

290 resynchronizer and holters), and prevent or treat postoperative AF. For instance, 41% of all
291 clinical trials are focused on palliating secondary effects of arrhythmias and avoid comorbidities
292 after surgery. Other clinical trials (19%) aim to investigate whether traditional AADs or other
293 known agents are more effective before or after electrical therapy or in combination with other
294 AADs. Yet other trials are focused on different formulations, doses, routes of administration or
295 small modifications in structure. As discussed in detail below, drug repurposing, also known as
296 repositioning or reprofiling, has played a key role in the history of antiarrhythmic drugs. Drug
297 repurposing still occupies an important place on anti-arrhythmic intervention, constituting almost
298 $\approx 30\%$ of the clinical trials during the last 10 years as shown in Figure 1D. Many of these
299 repurposing drugs are indicated for cardiovascular diseases (hypertension, diabetes,
300 cardiomyopathies, angina...), which have been demonstrated to have an antiarrhythmic effect or
301 to palliate the secondary arrhythmias induced by these diseases. It is impressive that all clinical
302 trials reported in the last 10 years on anti-arrhythmic therapies are not disease-specific, are
303 invasive or are only focused on palliating secondary effects or comorbidities. Critically, only
304 8.61 % of all studies aimed at developing innovative molecules that specifically target each type
305 of arrhythmia, highlighting those destined to AF, long QT syndrome (LQTS, catecholaminergic
306 polymorphic ventricular tachycardia (CPVT), bradycardia and ventricular arrhythmia as listed in
307 Figure 1D. Most of these innovative drugs are designed to modulate specific cardiac ion
308 channels like voltage gated potassium, sodium and calcium channels, and sarcoplasmic release
309 (RyR) channels, as listed in Figure 1D. Most are selective for modulating a single ion channel;
310 for example, F373280, a new therapy based on docohexaenoic acid (DHA) delivery, for the
311 maintenance of sinus rhythm after electrical cardioversion; BMS-919373, a highly functionalized
312 quinazoline, and potent I_{Kur} blocker used to treat atrial fibrillation; eleclazine, an inhibitor of

313 the late cardiac sodium current, is being tested for ventricular tachycardia and LQTS, specifically
314 LQTS type 3 (Bacic et al., 2017; El-Bizri et al., 2018); AP30663, a small conductance Ca^{2+} -
315 activated K^+ (I_{KCa}) channel blocker shown to prolong the atrial effective refractory period and
316 convert AF into normal sinus rhythm (Gal et al., 2020); nasal spray of etripamil (a calcium
317 channel blocker) is being investigated for the acute reduction of rapid ventricular rate in patients
318 with symptomatic AF or for the conversion of paroxysmal supraventricular tachycardia
319 (Abuelazm et al., 2023; Camm et al., 2023; Stambler et al., 2022); ARM210 (also known
320 S48168) is a potential disease-modifying therapy for CPVT as it repairs leaky RyR2 channels
321 (Marks, n.d.). Some compounds have multichannel blocking effects, like the intravenous HBI-
322 3000 studied for the conversion of recent onset AF (W. Chen et al., 2019; D. Guo et al., 2011).
323 Other compounds do not directly target ion channels but do so through secondary mechanisms,
324 including Oral LQT-1213 (Serum Glucocorticoid inducible Kinase 1) is indicated for congenital
325 LQTS Type 1, 2 or 3; CRD-4730 (Ca^{2+} or calmodulin-dependent protein kinase II) evaluated in
326 participants with CPVT or congenital heart defects, and OMT-28 (epoxyeicosanoid synthetic
327 analog) tested in patients with persistent AF (Berlin et al., 2020; Giannetti et al., 2023; M. Kim et
328 al., 2023). Yet other drugs such as OPC-108459 and HIP2001 and administered in patient with
329 paroxysmal and persistent AF, and oral CARDIX 101 under development for the treatment of
330 bradycardia, have unclear or unknown mechanisms or the mechanism has not been disclosed as
331 in the case of HSY244 for the treatment of AF (Linz et al., 2024). Natural products (1.23 %)
332 have also been tested as new drugs, such as Freeze-Dried California Table Grape, Wenxin
333 Granules, DH001 (active monomer from traditional Chinese medicine); and Tongmai Yangxin
334 Pill (TMYXP) (Dong et al., 2017; LIU et al., 2022; Shi et al., 2021). However, their molecular
335 mechanisms are unclear and they are not disease-specific.

336

337 The findings extracted from Figure 1 unequivocally indicate that the pursuit for advances in
338 antiarrhythmic therapies may be dwindling when juxtaposed with the progress observed in other
339 realms of scientific research. The data underscore the limited impact of innovative drugs focused
340 on the future antiarrhythmic pipeline and highlight the comparatively significant advances in the
341 field of anticoagulation associated with arrhythmias and drug repurposing. These observations
342 prompt a reevaluation of research priorities, urging a redirection of efforts towards areas that
343 show more promise for discovery and development of novel antiarrhythmic drugs. Altogether,
344 our compilation highlights the slow progress in advancing improved antiarrhythmic therapies
345 and underscores uncertainties regarding future developments in this field. Consequently,
346 developing new experimental and technological approaches is highly desirable and particularly
347 urgent to help overcome limitations. In the following sections we discuss the limitations of
348 antiarrhythmic drug discovery and how new tools can help accelerate progress.

349 **4. Human induced Pluripotent Stem Cell Technology**

350 Human induced Pluripotent Stem Cell (hiPSC) technology may revolutionize the field of
351 biomedical science allowing a “*clinical trial in a petri dish*” (Takahashi et al., 2007; Takahashi
352 & Yamanaka, 2006; Yamanaka, 2020). In the case of human cardiac diseases, the use of stem
353 cell technology in preclinical experimentation supposes a significant advance. Heart tissue from
354 human donors is difficult to obtain and does not regenerate, which has limited the development
355 and discovery of drugs. Although the use of murine models for human diseases is standardize in
356 biomedical research, interspecies differences make the study of arrhythmias difficult to translate
357 to the human (Doncheva et al., 2021). The heart rate of mice is ten times faster than human and
358 the action potential characteristics are vastly different due to the lack of functional expression of

359 some human ion channels in the mouse (Edwards & Louch, 2017). On the other hand,
360 heterologous cell lines (HEK, CHO, HL-1) lack the functional and structural characteristics of
361 human cardiomyocytes and present aneuploidies (Baik & Lee, 2017; R. Li & Zhu, 2022). hiPSCs
362 can be generated in nearly unlimited quantities- They can be cultured for long periods, and
363 cryopreserved. In addition, they are readily available in the market, and can be differentiated into
364 multiple cell lineages, including hiPSC-derived cardiomyocytes (hiPSC-CMs) (Shafa et al.,
365 2018). In addition, they can model human diseases better than other platforms like immortalized
366 human or transgenic cell lines and can be reprogrammed directly from patients' own cells. In
367 addition, the ability to differentiate hiPSCs into hiPSC-CMs provides a unique platform to study
368 cardiac diseases without cell limitation. Notably, hiPSC-CMs express a collection of ion
369 channels that enable them to generate cardiac-like action potentials. This offers huge advantages
370 over heterologous cell systems in which a single ion channel is tested (Cunningham et al., 2019;
371 Rogers et al., 2016). Moreover, iPSC-CMs can form electrically coupled monolayers and
372 engineered cardiac tissue constructs that can be used to quantify electrical impulse propagation
373 and study mechanisms of re-entrant arrhythmias (Jimenez-Vazquez et al., 2022).

374 During the last decade, attempts have been made to standardize the use of hiPSC-CMs for drug
375 discovery as well as the assessment of cardiotoxicity, which is a primary risk factor in cancer
376 drug development (Gintant et al., 2019; Sharma et al., 2018). hiPSC-CMs are central to the
377 Comprehensive in-vitro Proarrhythmia Assay (CiPA) consortium. CiPA was established in 2013,
378 as a step to confirm the results of *in-vitro* and *in-silico* tests on drug effects on multiple cardiac
379 ion channels and the cardiac AP. Such effects are focused on pro-arrhythmia and the potential to
380 generate Torsade de Pointes (TdP), a polymorphic ventricular tachycardia that can lead to SCD
381 (Sager et al., 2014; Strauss et al., 2019). It has the support of regulatory agencies, academic

382 laboratories and pharmaceutical companies (*Q&A ICH-Guideline E14/S7B Clinical and Non-*
383 *Clinical Evaluation EMA Document, see reference section*). New technologies as artificial
384 intelligence (AI) and deep learning are also helping to discern the risk of drug-induced
385 arrhythmia by analyzing features of *in-vitro* AP recordings in hiPSC-CMs that correlate with
386 clinical arrhythmia manifestations (Serrano et al., 2023). Ideally, some of the new candidate
387 drugs would move to start the different phases of clinical trials directly after checking their
388 effectiveness and toxicity in hiPSCs (Sharma et al., 2018). However, even the most common
389 hiPSC-CMs *in vitro* assays have important limitations that limit their full acceptance by
390 regulatory agencies, as well as scientific publications. Such limitations include the hiPSC-CMs'
391 lack host immune components and their fetal/neonatal cardiomyocyte-like phenotypes, with
392 paucity of important ion channels (e.g., I_{K1}) that make them unable to fully recapitulate drug
393 effects on adult human cardiomyocytes (da Rocha et al., 2017; X. Yang et al., 2022).

394 Despite the above limitations, hiPSC-CMs are a promising tool for drug discovery. In addition,
395 the use of this technology is not limited to testing new drugs, but also applies to disease
396 modeling, disease phenotype anticipation, reengineering previous drugs with less side effects and
397 personalized medicine (Correia et al., 2023). As reviewed recently by other authors (Matsa et al.,
398 2016; Pourrier & Fedida, 2020) (Musunuru et al., 2018), advances in hiPSC-CM research have
399 provided a platform to effectively study patient-specific heart disease *in vitro*. The use of patient-
400 specific hiPSC-CMs may be useful for basic science investigations, as well as for patient-specific
401 drug screening and personalized therapy. Several studies have focused on testing new anti-
402 arrhythmic drugs in hiPSC-CMs with promising results. For example, Dago et al 2022, showed
403 that the use of dapagliflozin and empagliflozin could be used as a new class of anti-arrhythmic in
404 heart failure by increasing sodium (I_{Na}) and inward rectifying potassium (I_{K1}) currents (Dago et

405 al., 2022). Apart from testing new drugs, the use of hiPSC-CMs is helping in reengineering
406 existing drugs with better therapeutic results and less side effects, as is the case of mexiletine in
407 LQTS3 (McKeithan et al., 2020).

408 Human iPSC-CMs serve not only to study diseases in the patient's own cells. Gene editing tools
409 like CRISPR/Cas 9 (Han et al., 2023), transcription activator-like effector nucleases (TALENs)
410 and zinc-finger nucleases (ZFN) (Hockemeyer et al., 2011; H. L. Li et al., 2015; Y. Wang et al.,
411 2014) are helping to develop new disease models and to generate isogenic hiPSC-CMs for
412 experimental controls (F. Guo et al., 2019). Wang et al 2014 reproduce patient phenotype of
413 LQTS by introducing dominant negative mutations in *KCNQ1* by ZFN (Y. Wang et al., 2014).
414 Gene editing helps also in the discovery of new treatments for cardiac pathologies. Nowadays,
415 variants of uncertain significance (VUSs) are emerging as an important challenge in clinical
416 genetics, with enormous implications for precision medicine (Fatkin & Johnson, 2020). VUSs
417 show no evidence of pathogenicity (Richards et al., 2015) but some health providers describe
418 VUSs as likely related to monogenic cardiovascular disorders such as cardiomyopathies and
419 rhythm disorders even though they do not meet clinical criteria (Muller et al., 2020). hiPSC-CMs
420 are then a good platform to study such variants. Garg et al observed that a VUS in *KCNH2*
421 (LQTS2) was pathogenic (Garg et al., 2018). The study of the molecular mechanisms of these
422 pathogenic variants in the same or different genes, help scientists to observe common
423 mechanisms to treat different diseases. Mutations in different genes or even different mutations
424 in the same gene can have different consequences at the molecular level, but still have the same
425 clinical outcome, e.g., cardiomyopathy (Spielmann et al., 2022). Patient-specific iPSCs offer the
426 opportunity to dissect mechanisms directly relevant to the patients' mutations (Campbell et al.,
427 2015; Ma et al., 2018). By virtue of having a perfectly matched genetic background, patient-

428 specific iPSCs can provide a model system that integrates all the genomic *loci* involved in the
429 response to medication (Carcamo-Orive et al., 2017). This is crucial as antiarrhythmic therapy
430 depends on the specific type of arrhythmia, its underlying cause, and individual patient
431 characteristics. Another great advantage of using patient specific iPSC-CMs is that they are an
432 unlimited resource to apply single cell omics assays, when it is almost impossible to obtain
433 cardiac tissue from patients. This opens a new world of treatments and breaks out the traditional
434 method of drug testing in the patient by trial and error. With patient-specific-iPSC-CMs, one can
435 test the cell response to different types of drugs at wide ranges of drug concentration (Theodoris
436 et al., 2021). Moreover, using omics one can identify new biomarkers and targets for disease
437 treatment. The combination of any given patient's unique clinical, genomic, proteomic and *in-*
438 *vitro* cellular characteristics obtained from hiPSC-CM experiments, may help the clinician in
439 making decisions regarding diagnosis, treatment, and prevention of human diseases, providing a
440 personalized treatment (Perry et al., 2021).

441 However, although the above approaches could lead to major advances, using iPSC-CM has
442 potential limitations that must be considered. An immature phenotype is the principal concern.
443 These cells are pro-arrhythmic due to their immature electrophysiological phenotype and cell
444 structure (Goversen et al., 2018) . In addition, the level of hiPS-CMs maturation determines drug
445 responsiveness in pre-clinical cardiotoxicity and pro-arrhythmia screening (da Rocha et al., 2017).
446 Also, the time to reprogram cells and the mix of cell types after differentiation (ventricular, atrial
447 and nodal cells) are a concern. In the past years, several methodologies have been developed to
448 solve their fetal-like phenotype. Some methods include long term culture (Kamakura et al., 2013;
449 Seibertz et al., 2023), addition of hormones (Parikh et al., 2017), and fatty acids to cell culture
450 media (Feyen et al., 2020; X. Yang et al., 2019), cell co-culture, use of extracellular matrix

451 (ECM) or biomaterials, and mechanical or electrical stimulation (Ronaldson-Bouchard et al.,
452 2018), and new platforms that try to recapitulate several of these methods are emerging. These
453 new platforms also include co-culture of different cell types, interactions of cells with the
454 microenvironment (cell-cell and cell-ECM interactions) and physiological cues, facilitating more
455 translational studies due to their higher similarity to the adult heart (Beauchamp et al., 2020;
456 Schmidt et al., 2023). hiPSC-CM monolayers are generally less mature than 3D constructs,
457 however they do show some promise in enabling the study of action potential propagation and
458 reentrant arrhythmias (da Rocha et al., 2017). On the other hand, it is expected that the new 3D
459 platforms would solve problems seen with 2D constructs. Some engineering heart tissues (EHTs)
460 are 3D scaffolds formed by hiPSC-CMs and extracellular matrix or biomaterials as hydrogels
461 (Eder et al., 2016). An example is the commercialized Biowire, where EHTs are electrically
462 stimulated, enabling cardiac maturation, with good results in cardiotoxicity testing (Feric et al.,
463 2019; Nunes et al., 2013). Microtissues are 3D models containing hiPSC-CM co-cultured with
464 fibroblasts and endothelial cells. Giacomelli et al have generated these cardiac microtissues with
465 excellent results probing them in the study of arrhythmogenic cardiomyopathy and LQTS2
466 (Giacomelli et al., 2020, 2021). However, microtissues cannot self-organize, they do not contain
467 vasculature, and cannot recapitulate the developing heart. In contrast, organoids are small 3D
468 self-organizing cellular aggregates containing multiple cell types that represent more structurally
469 accurate models of the human myocardium. Some authors have used organoids for drug
470 screening due to their similarity to an adult heart and as they contain cells from the 3 germ-layers
471 (Mills et al., 2019). Beyond organoids are the assembloids, which can combine organoids with
472 cells from diverse tissue lineages or from artificially assembling multiple organoids (Campostrini
473 et al., 2021; Ng et al., 2022). Assembloids reproduce the interactions among multiple sub-regions

474 and cell types. In cardiovascular diseases, assembloids could advance targeted, tissue-specific
475 drug treatment in scenarios where drugs differentially affect subsections of an organ or tissue, as
476 for example the atria and the ventricle (Schmidt et al., 2023). However, the use of this platform
477 has limitations as most organoid types resemble early stages of human heart during
478 morphogenesis. Finally, nowadays the use of organ-on-a-chip (OoC) technology that allows the
479 interaction of different cell types is taking relevance (M. B. Chen et al., 2013; D. Kim et al.,
480 2014; Picollet-D'hahan et al., 2021). OoCs are designed for the growth of multiple organ-
481 specific cell types in a fully integrated system, often with different cell types cultured in separate
482 compartments that are interconnected via perforated membranes or juxtaposed microchannels.
483 The approach allows co-culturing multiple cell lineages that underlie organ function and enables
484 fluid flow, and in some cases, mimicking stretch to further simulate the *in-vivo* environment.
485 This allows the administration of drugs to the “blood channel” of an OoC while observing the
486 effects on an adjacent “tissue channel,” recapitulating the *in-vivo* environment and adding power
487 to the model (Azizgolshani et al., 2021). However, OoCs are still under development and their
488 primary focus resides on drug cardiotoxicity screening (Y. Zhao et al., 2020). An upgrade version
489 of OoCs are the organoids in an OoC or body-on-a-chip. This revolutionary technique combines
490 3D models of organoids with a fully integrated and connected system, where changes can be
491 studied in a more complex microenvironment. A good example is the exposure to clomipramine
492 (a tricyclic antidepressant) in an OoC, composed of a liver organoid chamber and heart
493 organoids in the bottom chamber. Heart organoids presented impairments in cell viability,
494 cardiac beating and calcium activities, suggesting the hepatic metabolism-dependent
495 cardiotoxicity of clomipramine (Yin et al., 2021). This impressive multi-organoids-on-a-chip
496 system can recapitulate the complex process of drug metabolism at the multi-organ level. Skardal

497 et al 2020 developed a 3-tissue organoid-on-a-chip platform to test a multipanel of FDA-recalled
498 drugs, demonstrating that some of these drugs caused toxicity in liver and heart (Skardal et al.,
499 2020). Moreover, they went a step further to develop a 6-tissue body-on-a-chip platform where
500 they observed that capecitabine, an anticancer drug, must be metabolized in the liver to become
501 active. This effect generated secondary effects in other organoids as cardiac and lung constructs.

502 **5. Multi-Omics**

503 The use of OMICS has also contributed to revolutionize the field of drug discovery and drug
504 testing (N. Nguyen et al., 2022). In recent years, genomics, transcriptomics, proteomics, and
505 metabolomics platforms have been incorporated to the study of complex interactions in
506 biological systems. Moreover, these new tools break away from the traditional concept of one
507 drug, one target; i.e, a single molecular target with high selectivity to avoid other biological off-
508 targets. The approach is useful in monogenic diseases, where traditionally one gene mutation has
509 implied one phenotype. The majority of diseases are multifactorial or polygenic and need multi-
510 target drugs to be treated (Bolognesi & Cavalli, 2016). Each of the different omics is focused on
511 a regulatory process. Thus, genomics study DNA sequences and allelic variants in organisms by
512 sequencing. Genomics also includes epigenomics, which studies how the genome is modified
513 such that the DNA sequence does not change, but the organism's observable traits do
514 (Westerman et al., 2020). Epigenomics can also show the functional interaction among
515 regulatory genes and coding and non-coding regions. A step further, with an additive effect to
516 these techniques, is the study of RNA by transcriptomics. Transcriptomics can give information
517 about RNA structure, stability, variants, and alternative splicing (Litviňuková et al., 2020).
518 Following the central molecular biology dogma: after RNA, translation occurs. A more complex
519 omic is proteomics. Proteomics allows the study of changes in the levels and posttranslational

520 modifications of a protein in the organism (Alvarez-Franco et al., 2021; B. Liu et al., 2020).
521 Finally, metabolomics, which is gaining relevance in recent years, studies complex interactions
522 in the different cell compartments. Metabolites are the end-product of the cell and are involved in
523 processes like degradation, enzyme kinetics, transport, and secretion (H. Zhang et al., 2022).
524 However, although all omics are specialized in a part of a biological system, they are focused on
525 the generation of complex networks of genes, transcripts, proteins, or metabolites to characterize
526 cell types and also study normal and pathological conditions in a quantitative and qualitative
527 manner.

528 All omics are based on new technical platforms as Next-generation sequencing (NGS), RNA-
529 sequencing (RNA-seq), Chromatin-immunoprecipitation sequencing (ChIP-seq) and DNA
530 methylation sequencing (Methyl-seq), single cell sequencing, liquid chromatography and mass
531 spectrometry (LC-MS). All these new applied omics techniques generate large amounts of data
532 that need to be process and registered in databases. Several articles have extensively reviewed
533 the different types of databases (Matsa et al., 2016; Paananen & Fortino, 2020; Satam et al.,
534 2023). Other omics that are emerging in recent years are lipidomics (full characterization of
535 lipids); glycomics (study of glycans produced by cells under specified conditions), and
536 glycoproteomics (study of glycoproteins, glycan structure, and protein identity and
537 glycosilations). Nowadays, omics data help in pharmaceutical research. In the case of
538 arrhythmogenic diseases, the combination of omics with stem cell technology has helped in
539 diagnosis, drug discovery and treatment of diseases. As such, genomics helps in the
540 identification of mutations responsible of genetic disorders or genetic polymorphisms and can
541 predict prognosis, severity, and drug responsiveness (Wilson et al., 2015). Genomics also helps
542 in understanding pathogenesis (e.g., GWAS databases), patient stratification, and discovery of

543 putative drug targets or assessing the efficacy and toxicity of drugs at the genetic level. For
544 example, the identification by GWAS of new genes involved in AF (B et al., 2020). Another
545 example is the use of genomics in Brugada Syndrome, which has helped in the development of a
546 genetic risk score, due to the different *SCN5A* variants related to disease severity (Wijeyeratne et
547 al., 2020). Transcriptomics also serves as a platform for drug discovery and drug evaluation, as
548 well as to predict adverse drug target effects. Such is the case of the use of an agonist of PDGF
549 (Platelet-derived growth factor) that decreased arrhythmia incidence in dilated cardiomyopathy
550 caused by a Laminin A gene mutation (J. Lee et al., 2019). However, Transcriptomics goes a
551 step further as it can decipher disease mechanisms and the mode of action of drugs (Alexander-
552 Dann et al., 2018).

553 Although transcriptomic is the most readily used single-cell -omics level analysis, proteomics
554 and metabolomics are gaining force in the discovery and toxicity evaluation of drugs, as well as
555 identifying new biomarkers. Proteomics studies post-translational processes and the interactome,
556 helping identify molecular pathways like the ProteomicsDB database that also helped in drug
557 target identification (Samaras et al., 2020). Proteomics data also provide information for testing
558 drug targeting efficacy and safety, as well as protein toxicology. Chemoproteomics is a new
559 technology that combines mass spectrometry (MS) proteomics with chemical methods. In
560 chemoproteomics small molecules bind to protein targets, indicating the amount of drug
561 necessary for binding and what therapeutic effect it will produce. Moreover, the approach can
562 assess off-target interactions by determining drug selectivity (Jones & Neubert, 2017). Finally,
563 metabolomics has similar advantages as proteomics, but adding drug target discovery. An
564 example of these omics applied to the arrhythmogenic field is the identification of proteomic and
565 metabolite changes in Brugada patients with respect to control patients, identifying novel disease

566 biomarkers (Di Domenico et al., 2013). Although all omics are useful, focusing on a single omic
567 technique cannot elucidate the entire biological response to drug treatment. Then, the
568 combination of different omics in multi-omics or high-throughput technologies entails a better
569 understanding of drug related mechanisms (N. Nguyen et al., 2022). The birth of AI and machine
570 learning is also helping in processing the huge amounts of data obtained from omics. However,
571 the results derived from the use of techniques should be complemented necessarily by functional
572 studies to determine how individual genetic variants affect drug responses. Pharmacogenomics is
573 then related to personalized medicine, as each patient is unique due to personal SNPs (single-
574 nucleotide polymorphisms). These may induce patient variability in drug efficiency as described
575 for the various degrees of severity of Brugada syndrome (Di Domenico et al., 2013; Wijeyeratne
576 et al., 2020). Most AADs that target cardiac repolarization by blocking delayed rectifier K^+
577 current I_{Kr} (flecainide, amiodarone, dronedarone and sotalol) cause drug-induced TdP (Behr &
578 Roden, 2013).

579 The risk of developing LQTS or TdP can be influenced by genetic factors, particularly SNPs that
580 affect the function of cardiac ion channels. For example drug-induced LQTS due to
581 sulfamethoxazole antibiotic medication. Sesti and colleagues reported that a SNP in the *KCNE2*
582 gene encoding MiRP1 (T8A-MiRP1), a subunit of the hERG channels that has been associated
583 previously with inherited LQTS, underlies genetic predisposition of sulfamethoxazole-induced
584 LQTS (Sesti et al., 2000). Importantly, I_{Kr} in T8A-MiRP1 SNP patient was normal at baseline
585 but at least 4-fold more sensitive to therapeutic levels of sulfamethoxazole than wild type
586 channels (Sesti et al., 2000). Sulfamethoxazole speeded deactivation (closure) only of I_{Kr} formed
587 with T8A-MiRP1 SNP (Sesti et al., 2000). Hence, patients carrying these genetic variants may be
588 at a higher risk of developing drug-induced LQTS when exposed to sulfamethoxazole, as the

589 drug's effect on cardiac repolarization is amplified due to their underlying genetic predisposition.
590 This illustrates the importance of pharmacogenomics in predicting adverse drug reactions and
591 tailoring treatments to individual genetic profiles. For more examples, Dan et al 2012 provide a
592 summarized table of the different drugs and genes involved in the pharmacogenomics of anti-
593 arrhythmics (Dan et al., 2018).

594 **6. Computational Screening for Accurate Development of New Chemical Compounds**

595 Advancements in computational modeling in drug discovery have revolutionized the
596 pharmaceutical industry, accelerating the identification and development of novel therapeutics.
597 Traditional drug discovery methods are time-consuming and expensive, but computational
598 modeling expedites the process by predicting molecular interactions, identifying potential drug
599 targets, and optimizing compound structures (Sadybekov & Katritch, 2023; Sliwoski et al.,
600 2014). The process involves algorithms, simulations, and databases to simulate molecular
601 interactions, predict compound behaviors, and evaluate their efficacy and safety. This reduces
602 considerably the need for extensive laboratory testing and significantly decreases the time and
603 resources needed for drug discovery and basic science. Initially, researchers input structural data
604 of target molecules or biological systems into computer models. Molecular docking predicts how
605 small molecules (potential drugs) interact with target proteins, simulating their binding and
606 affinity (Gioia et al., 2017; Kitchen et al., 2004; Kontoyianni, 2017). Using molecular docking
607 software, the ligand's three-dimensional structure is virtually fitted into the binding site of the
608 target molecule, exploring various orientations and conformations. The software evaluates and
609 scores these ligand-protein interactions based on factors like binding energy, complementarity,
610 and predicted stability of the complex. Docking studies help identify potential drug candidates by
611 assessing their likelihood to bind to the target and modulate its activity. They guide medical

612 chemists by suggesting structural modifications to optimize binding affinity and specificity.
613 However, docking models have limitations like considering only the static structure of proteins
614 and simplifying the complexities of molecular interactions in living systems (Kolb et al., 2012).
615 Nevertheless, the combination of new and feasible molecules by docking with molecular biology
616 and STEM (science, technology, engineering and mathematics) technology will allow the
617 discovery of new drugs. Further, molecular dynamics simulations allow researchers to
618 understand the dynamic behavior of druggable molecules and their interactions with biological
619 targets at a level of detail that was once unimaginable (Ahmed et al., 2023; De Vivo et al., 2016;
620 Kuzmanic et al., 2020). This insight aids in designing more effective and specific drugs with
621 fewer side effects. However, as before, integrating experimental proof is crucial to validate and
622 enhance the reliability of the predictions generated through *in-silico* docking studies. For
623 instance, research indicates that flecainide and propafenone increase I_{K1} by reducing polyamine
624 blocking of the strong inward rectifier potassium channel Kir2.1 (Caballero et al., 2010; Gómez
625 et al., 2014). Structural modeling combined with experimental validation has illustrated that both
626 flecainide and propafenone bind to Kir2.1 through specific interactions with Cys311. Such an
627 interaction has facilitated the identification of the pharmacophore associated with drugs that
628 enhance Kir2.1 function (Caballero et al., 2010; Gómez et al., 2014). Similarly, investigations at
629 the atomic scale have delved into the structure-based molecular mechanisms of AADs.
630 Researchers employed Rosetta structural modeling, docking techniques, and molecular dynamics
631 simulations to scrutinize the interactions of AADs like flecainide, lidocaine, and ranolazine, with
632 the human voltage-gated sodium channel ($Na_v1.5$) (Bender et al., 2016; Meiler & Baker, 2006).
633 Those calculations unveiled pivotal drug binding sites within the pore lumen, capable of
634 simultaneously accommodating up to two drug molecules. Interestingly, molecular dynamics

635 simulations further elucidated a hydrophilic access pathway through the intracellular gate and a
636 hydrophobic access pathway via a fenestration situated between DIII and DIV of Na_v1.5 (P. T.
637 Nguyen et al., 2019). The assessment of AP within an *in-silico* modeling framework has also
638 proven to be a potent tool for early detection of drug-induced proarrhythmic risk. This evaluation
639 showcases its efficacy in discriminating torsadogenic compounds that impact the AP duration
640 (APD) across isolated endocardial, midmyocardial, and epicardial cells, along with inducing QT
641 prolongation in human ventricular action potential models (Romero et al., 2018).

642 Quantitative Structure-Activity Relationship (QSAR) models can be integrated in the workflow
643 analysis of chemical and biological properties to forecast a compound's activity (Lipinski et al.,
644 2001). Specially, QSAR models decipher the intricate relationship between a compound's
645 structure and its biological activity through computational analysis. By scrutinizing various
646 chemical descriptors—molecular size, shape, electronegativity, and more—alongside biological
647 properties like receptor affinity or enzyme inhibition. QSAR models predict how structural
648 modifications impact a compound's effectiveness or toxicity (Bradbury, 1995). These models
649 employ statistical techniques to generate equations correlating the chemical structure's
650 quantitative features with the observed biological activity, facilitating the prediction of untested
651 compounds' behavior. *In silico* methods accelerate drug discovery by reducing the number of
652 compounds requiring physical testing, optimizing lead compounds, and predicting potential side
653 effects. However, they rely heavily on the quality of input data and model accuracy (Holzinger et
654 al., 2019). Continuous advancements in computational power and algorithms enhance the
655 precision and efficiency of these techniques, reshaping the landscape of pharmaceutical research
656 and expediting the development of novel therapeutics. For example, QSAR plays a pivotal role
657 in addressing drug-induced TdP risks (Broccatelli et al., 2012; Das et al., 2023; Frid &

658 Matthews, 2010). QSAR models utilize large datasets, such as those resulting from compulsory
659 human ether-a-go-go-related gene channel (hERG) screening, to establish correlations between
660 molecular structures and biological activities. QSAR aids in predicting IC50 values for hERG
661 blockade, providing valuable insights into the potential cardiotoxic effects of drugs (Choi et al.,
662 2020; Wacker & Noskov, 2018). However, the evolution beyond traditional QSAR techniques,
663 with modern Machine Learning (ML) algorithms, particularly eXtreme Gradient Boosting
664 (XGBoost), demonstrates superior accuracy in determining hERG blockade and paves the way
665 for more advanced predictive models in drug development and safety assessment (Wacker &
666 Noskov, 2018; X. Yang et al., 2023).

667 AI and machine learning have become pivotal in revolutionizing drug development in the future
668 (Sarkar et al., 2023a). These are technologies based on vast datasets and advanced algorithms;
669 they predict biological activities, and expedite drug discovery potentially reducing costs and
670 timelines. Through pattern recognition and analysis, AI models can sift through massive amounts
671 of biological, chemical, and clinical data to identify potential drug candidates, predict their
672 efficacy, optimize molecular structures, and even anticipate adverse effects (Mullowney et al.,
673 2023; X. Yang et al., 2023; Z. Zhu et al., 2022). These models learn from diverse data sources
674 (e.g., omics information, protein structures, drug interactions, and patient data) to suggest
675 promising compounds, assisting in virtual screening, and predicting a compound's potential
676 activity against a target. For instance, AI and data mining helps in all omic data processing,
677 contributing to the new field of pharmacogenomics and personalized medicine, as has been done
678 in type 2 diabetes (Allesøe et al., 2023). Virtual screening, empowered by machine and deep
679 learning, rapidly analyzes vast chemical libraries to identify potential candidates for further
680 experimental validation processes to ensure the efficacy and safety of identified compounds. Its

681 integration into drug development pipelines has revolutionized early-stage screening, offering a
682 more efficient pathway for identifying promising drug candidates (Chan et al., 2019; Sarkar et
683 al., 2023a). Therefore, these technologies hold immense promise, despite facing challenges like
684 data quality representation and ethical considerations, reshaping drug development and
685 potentially expediting the delivery of safer and more effective treatments to patients worldwide
686 (L. K. Vora et al., 2023). In summary, the integration of computational modeling techniques has
687 greatly enhanced the efficiency and effectiveness of drug discovery, promising a future where
688 the development of new therapies is not only faster but also more precise and tailored to
689 individual patient needs. However, computational technologies are not understood alone. They
690 need validation in biological samples that test functional outcomes like electrophysiology in the
691 case of arrhythmogenic diseases and drug therapy.

692 **7. High-Throughput Screening Electrophysiological Platforms**

693 Drug discovery in the cardiovascular diseases field is constantly changing and has been evolving
694 with emerging technologies and methodologies to meet challenges and needs. The recent
695 evolution of High-Throughput Screening (HTS) is playing an essential role in drug discovery for
696 antiarrhythmic therapy by contributing to increase success rates in the identification and
697 development of effective and safe potential drug candidates (Bunch et al., 2023; Satam et al.,
698 2023; Wilson et al., 2015). The use of HTS has revolutionized traditional drug development in
699 cardiac diseases by expediting the efficient identification of lead compounds, optimizing their
700 properties, and enhancing our understanding of the complex mechanisms underlying cardiac
701 arrhythmias and potential drug interactions (Bruyneel et al., 2018; da Rocha et al., 2017). A good
702 example is the study by Sharma *et al.*, where using hiPSC-CMs and applying various HTS
703 assays they identified a signaling pathway by which different tyrosine kinase inhibitors (TKI),

704 used in oncology, produce cardiovascular side effects ranging from induced arrhythmias to heart
705 failure. Increased cardioprotective signaling of this pathway identified with exogenous insulin or
706 insulin-like growth factor-1 (IGF-1) enhanced the viability of hiPSC-CMs during co-treatment
707 with cardiotoxic TKI. This approach provided the unexpected insight that cardiotoxicity and
708 arrhythmias induced by certain anticancer drugs can be alleviated via cardioprotective
709 insulin/IGF signaling (Sharma et al., 2017). HTS allows for the rapid and simultaneous screening
710 of large compound libraries against multiple targets implicated in the complex mechanisms of
711 arrhythmogenesis. Thus, HTS accelerates the identification of compounds with potential
712 antiarrhythmic properties fostering innovation in drug discovery beyond traditional targets
713 (Wells et al., 2019). HTS significantly reduces the time and resources required by automating the
714 screening process in a short period. For example, Glazer and colleagues used a high-throughput
715 automated patch-clamp system to study the function of the 83 variants in *SCN5A* gene associated
716 with Brugada Syndrome. They reclassified the variants with functional data expressed in HEK
717 cells (Glazer et al., 2020). This efficiency is particularly valuable in the context of arrhythmia
718 stratification and antiarrhythmic therapy, where rapid intervention may be critical (Al-Khatib et
719 al., 2018). For example, a study established a high-throughput drug testing system on 13
720 different compounds using human iPSC derived atrial-like myocytes for drug discovery in AF
721 (Honda et al., 2021). HTS assays facilitate the optimization of lead compounds, which can then
722 be further investigated for enhanced doses, efficacy, and selectivity, improving the candidate's
723 therapeutic profiles. These assays can also be employed to assess potential cardiotoxic effects
724 early in the drug development process, helping to prioritize compounds with a lower risk of
725 adverse cardiac effects (Krishna et al., 2021). HTS allows the use of patient-specific iPSC
726 models, contributing to the development of personalized antiarrhythmic therapies that consider

727 individual variations in drug response, (del Álamo et al., 2016) as described in detail in previous
728 sections. The complementary use of hiPSCs and HTS technologies offers great versatility and
729 advantages for arrhythmia research; e.g., one can validate the targets involved in the
730 development of arrhythmias identified by omics, as well as test new drugs designed against these
731 specific targets designed by computational modeling as explained in previous sections.
732 Evidently, not only has HTS benefited greatly from hiPSC technology, but many of these
733 technologies have been designed specifically for application in hiPSC-CMs and not in animals or
734 heterologous expression systems as previously shown. Priority is now being given to the HTS
735 technologies using automated electrophysiological platforms. Automated patch-clamp systems
736 can rapidly screen many genetic variants and/or compounds, and analyze their effects on
737 multiple ion channels aiding in the identification of potential candidates (Obergrussberger et al.,
738 2021; Walsh, 2015). For example, a study was able to test the effects of 26 drugs and 3 drug
739 combinations on two iPSC-CM lines using high-throughput voltage-sensitive dye and
740 microelectrode-array assays. Drugs were studied for the CiPA initiative and results were
741 compared with clinical QT prolongation and TdP risk (Blinova et al., 2017). Automated systems
742 often allow for parallel recordings from multiple cells or channels simultaneously. This enables
743 researchers to study the effects of compounds on different cell types or ion channels more
744 efficiently (Obergrussberger et al., 2021). Automated patch-clamp systems offer various
745 advantages with respect to manual patch-clamp, such as much faster experimental rates,
746 consistency, reproducibility, continuous recording, user-friendly interfaces, customization, and
747 flexibility to design experiments (Obergrussberger et al., 2021). For example, a study validated
748 state dependence and subtype selectivity of reference calcium channel modulators (nifedipine,
749 BAY K8644, verapamil, mibefradil, and pimozone) on human Cav1.2, Cav2.1, Cav2.2, and

750 Cav3.2 channels using automated electrophysiology assays (Kuryshv et al., 2014). It is
751 important to note that manual patch-clamp techniques still have their place, especially in
752 situations where fine control, manual dexterity, or specific experimental conditions are crucial.
753 Non-Invasive electrocardiographic imaging (ECGI), which allows the reconstruction of high-
754 resolution cardiac electrical activity maps, enables the assessment of drug-induced changes in
755 cardiac electrophysiology (Rudy, 2013). Experimental cardiac optical mapping is the gold
756 standard for measuring complex electrophysiology in *ex-vivo* and *in-vitro* heart preparations.
757 Optical mapping uses voltage-sensitive or calcium-sensitive fluorescent dyes to visualize and
758 measure the dynamics and drug-induced changes in electrical wave propagation on both the
759 surface of an animal heart (P. Lee et al., 2019) and hiPSC-CM monolayers (W. Liu et al., 2023).
760 Microelectrode array (MEA) platforms can monitor the electrical activity. In 2D iPSC-CMs
761 monolayers, recording the field potential duration (FPD), an electrical signal similar to the ECG.
762 This technique also provides insights into drug-induced changes in cardiac rhythms (del Álamo
763 et al., 2016; S. R. Zhao et al., 2022). In addition, techniques for the analysis of
764 electrophysiological function in cardiac organoids, 3D culture systems, and organ-chips are
765 being developed, which should provide more relevant insights compared to traditional cell
766 culture models (X. Zhang et al., 2016). During the last decade, advanced automated microscopy
767 techniques are being incorporated simultaneously to control and monitor the electrical activity
768 and calcium handling of specific cardiac cell types for studying drug effects at a cellular and
769 subcellular level (Dvinskikh et al., 2023; Huebsch et al., 2015). HTS generates large datasets that
770 can be integrated with computational and bioinformatics approaches, providing a systems-level
771 understanding of drug effects on cardiac electrophysiology. The integration of all such
772 electrophysiological data sets with multi-omics and bioinformatics approaches (machine learning

773 algorithms and AI) can help identify potential antiarrhythmic therapies (Galappaththige et al.,
774 2022; Sarkar et al., 2023b; Trayanova et al., 2021). These emerging HTS electrophysiological
775 technologies offer more precise, relevant, and efficient ways to evaluate the antiarrhythmic
776 potential of new drugs, ultimately enhancing drug safety assessments and reducing the risk of
777 adverse cardiac events during drug development and clinical use.

778 **8. Exploring Drug Repurposing for Arrhythmia Treatment**

779 Developing a new drug from scratch is a time-consuming and expensive process (Kale et al.,
780 2022). To move forward, researchers have to consider and explore other approaches like drug
781 repurposing. Drug repurposing involves identifying novel therapeutic uses for existing drugs
782 outside their originally intended scope (Abdelsayed et al., 2022; Choudhury et al., 2022; Gelosa
783 et al., 2020). The strategy offers a cost-effective alternative and leverages the extensive
784 knowledge available about a drug's safety profile, pharmacokinetics, and mechanisms of action,
785 potentially expediting the development process (Kale et al., 2022). Known safety profiles of
786 repurposed drugs can mitigate the risk of unexpected adverse effects. This advantage is
787 particularly crucial in cardiac care, where the consequences of adverse reactions can be severe
788 (Abdelsayed et al., 2022; Gelosa et al., 2020; Saljic et al., 2023). Moreover, repurposed drugs
789 often possess mechanisms of action that can address multiple pathways involved in
790 arrhythmogenesis. This multifaceted approach may enhance therapeutic efficacy compared with
791 traditional single-target drugs (Wasim et al., 2023). In addition, HTS technology can also be used
792 to screen existing drug libraries to identify compounds with unforeseen antiarrhythmic
793 properties, facilitating drug repurposing strategies (Abdelsayed et al., 2022). There are several
794 interesting examples of repurposed drugs for arrhythmias. For example, originally amiodarone
795 was developed as an antianginal agent owing to its vasodilating effect; however, amiodarone was

796 repurposed as an antiarrhythmic drug due to its potent effect on various ion channels
797 (Tavolinejad et al., 2019). It is now widely used to treat life-threatening ventricular arrhythmias.
798 A derivative of amiodarone, dronedarone, was developed to reduce amiodarone's side effects
799 while retaining its antiarrhythmic properties and is used in the management of AF (Pannone et
800 al., 2021; Vamos & Hohnloser, 2016). Other examples are verapamil and diltiazem, calcium
801 channel blockers, initially designed for hypertension and angina treatment. These drugs have
802 shown efficacy in certain supraventricular arrhythmias by modulating calcium currents in the
803 heart (Godfraind, 2017). A more recent example is ranolazine which was developed initially as a
804 metabolic modulator and approved as an antianginal agent; however, it was also identified as an
805 inhibitor of the cardiac late Na^+ and hERG currents. The latter actions underlie ranolazine's
806 antiarrhythmic effects on both supraventricular and ventricular arrhythmias. However, despite
807 initial enthusiasm, ranolazine is only authorized as a second-line treatment in patients with
808 chronic angina pectoris, notwithstanding its antiarrhythmic properties (Frommeyer et al., 2016;
809 Rouhana et al., 2021; Shenasa et al., 2016). In summary, while drug repurposing holds great
810 promise for arrhythmia treatment, challenges persist. Rigorous clinical trials are essential to
811 establish the safety and efficacy of repurposed drugs in specific arrhythmia subtypes.
812 Additionally, identifying suitable candidates for repurposing and understanding the precise
813 mechanisms of action remain ongoing challenges.

814 **9. Gene Therapy Approaches**

815 Recombinant adeno-associated (rAAV) viruses have been successfully used as the selected
816 vehicle for viral gene delivery in a wide range of clinical applications in multiple diseases
817 (Mendell et al., 2021). In the last decades, AAV-gene delivery progressed to FDA-approved
818 clinical trials with a good safety profile and promising results in the treatment of genetic diseases

819 such as hemophilia, lipoprotein lipase deficiency (LPLD), inherited retinal disease (IRD) and
820 spinal muscular atrophy (SMA) (Gaudet et al., 2013; Mingozzi & High, 2011; Nathwani et al.,
821 2011). However, the use of AAV-gene therapy has limited success to prevent and treat cardiac
822 disorder (Bass-Stringer et al., 2018a; Ishikawa et al., 2018a). Intracoronary infusion of AAV1
823 encoding SerCA2a (a phase iib) failed to demonstrate beneficial results of AAVs-based gene
824 therapy in patients with heart failure (Greenberg et al., 2016). There are still numerous
825 challenges that need to be resolved, such as the inability of rAAVs to effectively target specific
826 tissues, preexisting neutralizing antibodies in human populations, the wrong molecular targets or
827 inadequate doses administered (Shen et al., 2022). However, the interest for clinical rAAV-gene
828 transfer approaches to treat various disorders in other tissues has propelled growing interest and
829 progress in utilizing rAAVs for cardiac disorders. Gene therapy has the potential to correct the
830 underlying genetic defects that contribute to the development of arrhythmias rather than simply
831 alleviating symptoms, offering long-term, precise, and targeted treatment (Bass-Stringer et al.,
832 2018b). However, gene therapy for cardiac arrhythmias is still in a research-and-development
833 phase, and there are significant challenges to overcome before it can become a standard
834 treatment. As described above, AAVs are one of the most widely used gene delivery systems;
835 however, it presents specific limitations for cardiac gene therapy (Ishikawa et al., 2018b; Shen et
836 al., 2022). AAVs DNA capacity is limited to < 4.8 kb for efficient packaging, which means that
837 they can only carry and deliver genes of relatively small size. This is a major limitation for the
838 treatment of arrhythmias since cardiac ion channel encoding genes are usually very large.
839 Furthermore, achieving uniform, efficient, and specific transduction in cardiac cells can be
840 challenging and AAVs tend to accumulate in other tissues, especially liver, leading to adverse
841 effects. CRISPR technology is therefore considered for gene therapy in certain instances,

842 although it has its own limitations. Despite such limitations, AAVs remain a valuable option in
843 cardiac gene therapy, especially in preclinical research and early clinical trials.

844

845 Similarly, RNA-based therapies have emerged as a promising avenue in drug development for
846 cardiac diseases. Specifically, approaches like RNA interference (RNAi) and antisense
847 oligonucleotides (ASOs) offer potential treatments in cardiovascular disease (Crooke et al.,
848 2021). Many microRNAs or long noncoding-RNAs (lncRNAs) have been suggested to
849 potentially enhance cardiac activity in acute myocardial infarction, fibrosis, hypertrophy or heart
850 failure among others (Lucas et al., 2018; Lucas & Dimmeler, 2016). A further successful concept
851 of cardiovascular cell delivery using AAV was achieved using two proliferative miRNAs miR-
852 500 and miR-199a to promote cardiomyocyte regeneration and recover cardiac function after
853 myocardial infarction in mice (Eulalio et al., 2012). Similarly, miR-1 expression demonstrated a
854 potential novel therapeutic strategy to reverse pressure-induced cardiac hypertrophy and prevent
855 maladaptive cardiac remodeling (Karakikes et al., 2013; Luo et al., 2018). Over the past decade,
856 numerous oligonucleotide-based therapies have been developed utilizing LNA-modified
857 chemistries to modulate cardiac miRNAs. AntagomiRs and locked nucleic acid (LNA) antimiRs
858 stand out as prominent examples in the category of miRNA inhibitors (Krützfeldt et al., 2005).
859 Dysregulated miRNAs can contribute to the development or progression of cardiovascular
860 pathological conditions by promoting harmful processes and antimiRs are therapeutic molecules
861 designed to inhibit the function of specific miRNAs (Rupaimoole & Slack, 2017). LNA antimiRs
862 are an advanced form, chemically modified for greater stability and stronger binding to target
863 miRNAs (Samolovac & Hinkel, 2022). By blocking miRNA function, LNA antimiRs offer a
864 promising approach to treating cardiovascular diseases by potentially reversing damage caused

865 by abnormal miRNA activity (Samolovac & Hinkel, 2022). For instance, the therapeutic
866 potential of miR-15 as a target for manipulating cardiac remodeling and function in ischemic
867 injury has been validated (Hullinger et al., 2012). Additionally, therapeutic inhibition through
868 LNA-based antimiRs targeting miR-208a has shown improvements in cardiac function and
869 increased survival during heart failure (Montgomery et al., 2011). Another observation is that
870 inhibiting the entire miR-34 family reduces cell death and fibrosis following myocardial
871 infarction (Bernardo et al., 2012; Y. Yang et al., 2015). These advancements underscore the
872 growing significance of LNA-modified chemistries and antimiRs in the development of
873 oligonucleotide-based therapies, particularly in the context of cardiac miRNA modulation.
874 Altogether, these RNA-based therapies hold promise due to their specificity and potential for
875 personalized medicine. By targeting specific genes or molecular pathways implicated in cardiac
876 diseases, they offer a tailored approach to treatment. Ongoing research aims to refine these
877 therapies to enhance their efficacy, reduce off-target effects, and bring forth safer and more
878 efficient treatments for multitude of cardiac disorders (Cornu et al., 2017; Dhakne et al., 2023;
879 Mann et al., 2002; Sasso et al., 2022).

880
881 In proof-of-concept studies, Nelson et al., and Tabebordbar et al. used AAV9 to deliver the
882 CRISPR/Cas9 gene-editing system to young mice with a mutation in the gene coding for
883 dystrophin deficiency in patients with Duchenne muscular dystrophy (DMD) (Nelson et al.,
884 2019; Tabebordbar et al., 2021). Gene editing partially restored dystrophin protein expression in
885 skeletal and cardiac muscle and improved skeletal muscle function. rAAV-delivery of
886 CRISPR/Cas9 or other enzymes to perform genome editing in mouse cardiomyocytes or hiPSC-
887 CMs (as previously discussed) is a powerful tool in both gene therapy and generating new

888 models. Novel Myo-AAV capsid has been used to achieve gene expression of CRISPR-based
889 gene therapy treating dilated cardiomyopathy (Grosch et al., 2023). Thus, gene-editing systems
890 elude any complication derived from vector size and can theoretically be applied to edit any gene
891 across diverse genetic backgrounds. This technology could offer a suitable platform in treating
892 cardiac diseases whose pharmacological spectrum fails in reducing arrhythmias.

893 **10. Peptide-based treatment, new antiarrhythmic modality**

894 Sudden cardiac death in children and young adults is a relatively rare but tragic event whose
895 molecular pathophysiology is unknown and treatment is inadequate (Mazzanti et al., 2020;
896 Moreno-Manuel et al., 2023). The identification of the interaction at the molecular level of the
897 main sodium channel ($\text{Na}_v1.5$) with the strong inward rectifying potassium channel (Kir2.1) in
898 the control of cardiac excitability and impulse conduction (Milstein et al., 2012) has opened a
899 new paradigm for drug discovery and treatment of arrhythmias and SCD. Kir2.1 and $\text{Na}_v1.5$
900 form "channelosomes" that are anchored together at their eventual membrane microdomains by
901 physically interacting via specific PDZ binding domains in their respective COOH terminal with
902 scaffolding proteins like SAP97 and $\alpha1$ -syntrophin (Gillet et al., 2015; Milstein et al., 2012;
903 Petitprez et al., 2011). Certain loss-of-function Kir2.1 mutations can also reduce $\text{Na}_v1.5$ function
904 in Andersen-Tawil Syndrome Type 1 (ATS1), a rare but potentially lethal inheritable cardiac ion
905 channel disease (Cruz et al., 2023; Macías et al., 2022; Moreno-Manuel et al., 2023). For
906 example, arrhythmias associated with a trafficking deficient mutation ($\Delta314-315$) in Kir2.1 alters
907 both I_{K1} and I_{Na} (Macías et al., 2022). Similarly, another loss of function Kir2.1(C122Y)
908 mutation that enables channel trafficking to the membrane but alters channel structure and
909 biophysics also reduces both I_{K1} and I_{Na} leading to slow ventricular conduction and arrhythmias
910 in ATS1 (Cruz et al., 2023). In many of these patients, the treatment provided by clinical

911 guidelines is based on combinations of β -blockers and traditional class 1C AADs like
912 flecainide. . Such treatments are empirical, subject to trial and error and may even be
913 proarrhythmic, likely because they impair sodium channel function (Kukla et al., 2014; Mazzanti
914 et al., 2020; Tristani-Firouzi & Etheridge, 2010). Therefore, the development of advanced and
915 targeted drug therapies based on small peptides that combine the elements necessary to transport
916 and anchor Kir2.1 and $\text{Na}_v1.5$ to the cell membrane could have an impact in treating cardiac
917 diseases related to ion channel remodeling. Patients with cardiomyopathy of DMD are at risk of
918 developing life-threatening arrhythmias because of ion channel remodeling that reducing both I_{Na}
919 and I_{K1} (Jimenez-Vazquez et al., 2022). Interestingly, transfecting just one component of the
920 dystrophin protein complex ($\alpha1$ -syntrophin) restored channelosome function, increasing I_{Na} and
921 I_{K1} densities in hemizygous iPSC-CMs from a DMD patient (Jimenez-Vazquez et al., 2022).
922 Thus, reimagining antiarrhythmic pharmacotherapy by developing bold, and tailored peptidic
923 solutions that restore channelosome dysfunction may have a powerful impact in treating a whole
924 spectrum of cardiac arrhythmias, from the molecule to the bedside. The approach could offer
925 improved efficacy and safety compared to conventional AADs, and may target neurological
926 disorders, cardiovascular diseases or even certain types of cancer.

927 A new class of peptidic agents, known as peptibodies is emerging. Peptibodies are chimeras
928 generated as fusion proteins of the fragment crystallizable (Fc) domain of the human
929 immunoglobulin G (IgG) with a bioactive “warhead” peptide (Cavaco et al., 2017; Shimamoto et
930 al., 2012). Peptibodies combine the biologic/therapeutic activity of a given peptide, with the
931 stability of monoclonal antibodies. They are stable and safe molecules that are developed as
932 viable clinical therapeutics. For instance, the first peptibody in clinical use is Romiplostim,
933 which is approved for the treatment of immune thrombocytopenic purpura (Hubulashvili &

934 Marzella, 2009). Romiplostim is composed of thrombopoietin mimetic peptides fused to the C
935 terminus of the Fc region of human IgG (McElroy et al., 2015; Molineux, 2011; Molineux &
936 Newland, 2010; Nichol, 2006; B. Wang et al., 2004). New studies have proposed the peptibody
937 technology to selectively design peptides that bind to and modulate the function of specific ion
938 channels involved in arrhythmogenesis (Calvo et al., 2018; Chidipi et al., 2022; Ehrlich et al.,
939 2008; Heijman et al., 2018). Specially, in persistent AF, the acetylcholine activated inward
940 rectifier potassium current (I_{KACH}) is constitutively active, behaves as a background potassium
941 inward rectifier channel, and can thus contribute to the initiation and maintenance of the
942 arrhythmia (Dobrev et al., 2005; Heijman et al., 2018). Since I_{KACH} is mainly expressed in the
943 atria and is largely absent from the working ventricular myocardium, it has been proposed that
944 blocking I_{KACH} can be an atrial-selective rhythm control pharmacotherapy (Calvo et al., 2018;
945 Ehrlich et al., 2008; Heijman et al., 2018). An I_{KACH} blocking peptibody (Fc-TP) was engineered
946 as a fusion protein between the Fc fragment of the human IgG1 and a tertiapinQ peptidotoxin
947 (TP) originally isolated from the venom of the European honey bee (Drici et al., 2000)). Patch-
948 clamping experiments showed that Fc-TP was ~300-fold more potent than TP alone, which could
949 be due to an increased stabilization between the peptibody and I_{KACH} . Interestingly, the peptibody
950 blocked carbachol-activated I_{KACH} in atrial tissue reducing inducibility of AF in aged mice while
951 minimizing off-target effects (Chidipi et al., 2022), but it did not affect the potassium current in
952 ventricular myocytes. Therefore, the advancement in designing peptibodies to target and
953 modulate ion channels implicated in arrhythmias represents a step forward in the development of
954 next-generation antiarrhythmic modalities with enhanced specificity and reduced adverse effects
955 for a variety of diseases.

11. Advancements in Drug Delivery

956
957 Traditional systemic drug administration can result in low drug concentrations at the heart and
958 potential side effects in non-cardiac tissues. Ensuring effective delivery of AADs to cardiac
959 tissue remains a critical challenge (Nadimi et al., 2018). Recent advancements in drug delivery
960 technologies are revolutionizing the landscape, offering new hope for improved therapeutic
961 outcomes. Targeted drug delivery systems aim to overcome these limitations by selectively
962 delivering medications to the affected cardiac tissue (Omidian et al., 2023). Development of
963 nanoscale drug delivery systems offers unique advantages. Nanoparticles Metal-, lipid-, and
964 polymer-based nanoparticles represent ideal materials for use in cardiovascular therapeutics
965 allowing enhanced drug stability, controlled release, and improved bioavailability (Qian et al.,
966 2023). Nanoparticles can be engineered to allow encapsulated antiarrhythmic drugs navigate
967 through the circulatory system and reach specific heart tissues (Nadimi et al., 2018; Z. Wang et
968 al., 2022; F. Yang et al., 2022) . For example, a study demonstrated that liposomal amiodarone
969 augments antiarrhythmic effects and reduces hemodynamic adverse effects in an
970 ischemia/reperfusion rat model (Takahama et al., 2013). Many studies have reported the
971 application of different nano-drug delivery systems charged with botulinum toxin, CaCl₂; L-
972 glutamate, budesonide, carvedilol, and N-isopropyl acrylamide monomer (Z. Wang et al., 2022)
973 in the treatment of AF. Such precision minimizes off-target effects and enhances therapeutic
974 efficacy. Moreover, surface modifications can enable nanoparticles to actively target areas such
975 as inflammation or fibrosis within the heart (Omidian et al., 2023). Implantable devices, such as
976 drug-eluting stents and patches, provide a localized and sustained release of antiarrhythmic
977 medications (Adhami et al., 2023; Fayzullin et al., 2021). These devices can be strategically
978 placed in or around the heart, ensuring continuous drug delivery to the affected area. For

979 instance, drug-eluting stents, have been designed to release medications directly into the
980 coronary arteries, reducing the risk of reoccurrence of arrhythmias following interventions like
981 catheter ablation (Adhami et al., 2023). The use of drug-eluting stents, among myocardial
982 infarction patients with AF has increased over time (A. N. Vora et al., 2023). In addition,
983 innovations in electro-responsive drug delivery systems involve the incorporation of smart
984 materials that respond to changes in the electrical environment of the heart. These systems can
985 release drugs in response to specific cardiac conditions, offering a real time and on-demand
986 therapeutic approach (Y. Zhao et al., 2016). For example, several hydrogels with conductive
987 properties have been designed to restore the electrical impulses to the heart, preventing further
988 remodeling and ventricular dysfunction after myocardial infarction (Tapeinos et al., 2022).

989
990 3D printing has emerged as a customized transformative technology allowing for the creation of
991 intricately designed structures and personalized medications. 3D printing enables the fabrication
992 of intricate drug formulations with precise control over drug release kinetics. Antiarrhythmic
993 medications can be embedded within biocompatible materials, such as polymers, in a controlled
994 and layered fashion (Vaz & Kumar, 2021). This design allows for sustained and targeted drug
995 release, ensuring optimal therapeutic concentrations in the affected cardiac tissue. For example,
996 the production of 3D-printed preparations of high-quality filaments containing amiodarone and
997 dronedarone have been described in the literature (Matijašić et al., 2019; Roulon et al., 2021). A
998 recent study also prepared propranolol hydrochloride gummy chewable tablets tailored for
999 children by semisolid extrusion 3D printing technology to meet personalized medicine needs in
1000 pediatrics (C. Zhu et al., 2022). 3D printing also facilitates the incorporation of multiple
1001 medications into a single, complex structure. This capability is particularly valuable in

1002 antiarrhythmic therapy, where combination drug regimens may be more effective (Lu et al.,
1003 2023). The versatility of 3D printing extends to the creation of implantable devices specifically
1004 designed for antiarrhythmic drug delivery. Implantable patches, stents, or microstructures can be
1005 customized to fit the unique anatomy of the heart, offering localized and sustained release of
1006 medications (Domsta & Seidlitz, 2021, 2021; Lu et al., 2023). These devices can be strategically
1007 placed to deliver drugs directly to the affected areas, improving the precision of treatment and
1008 reducing the risk of adverse effects. There are challenges related to 3D printing, which include
1009 ensuring the biocompatibility of printed materials, refining printing techniques for
1010 pharmaceutical applications, and navigating regulatory pathways. While these new drug delivery
1011 technologies hold immense promise, several challenges must be addressed to bring this
1012 technology to widespread clinical use. Optimizing biocompatibility, long-term stability, and
1013 scalability of these technologies remains a focus of ongoing research.

1014 **12. Concluding Remarks**

1015 Current antiarrhythmic therapies have limited efficacy and are frequently associated with adverse
1016 effects. Alarming, while the number of new therapies under investigation in other fields is
1017 growing exponentially, the number of novel antiarrhythmic targets and agents in the
1018 development pipeline has decreased substantially during the last few decades due to conceptual,
1019 regulatory and financial considerations (Saljic et al., 2023). Catheter ablation significantly
1020 contributes to the management AF, particularly in patients who are refractory or intolerant to
1021 antiarrhythmic drugs (Chugh et al., 2014; Parameswaran et al., 2021). The CABANA (Catheter
1022 Ablation vs Anti-arrhythmic Drug Therapy for Atrial Fibrillation Trial [CABANA];
1023 NCT00911508) trial's findings are particularly notable, demonstrating the effectiveness of
1024 catheter ablation in reducing the recurrence of AF and symptomatic episodes compared to drug

1025 therapy over a five-year follow-up period (Poole et al., 2020). It is crucial to consider not only
1026 the physical outcomes but also the impact of interventions such as catheter ablation on mental
1027 health in patients with AF. ANZCTR trial data (ACTRN12618000062224) suggest that catheter
1028 ablation may lead to greater improvements in markers of psychological distress, specifically
1029 symptoms of anxiety and depression, compared to medical therapy alone in individuals with
1030 symptomatic AF (Al-Kaisey et al., 2023). Nevertheless, it is not a universally applicable solution
1031 and the proposition of subjecting over 46 million AF patients to one or more ablation procedures
1032 would be exceedingly unreasonable. Consequently, arrhythmia treatment poses a significant
1033 challenge in the realm of cardiovascular health, prompting the need for alternative approaches.
1034 This has a point of complexity given that the heart is difficult to access, donors are limited, and
1035 data from rodent models are hard to extrapolate because the cardiac electrophysiological
1036 characteristics of small animals are significantly different from humans. This forces the use of
1037 large animals such as sheep, dogs, or pigs that have major cost and ethical limitations. Yet,
1038 disparities between animals and humans can confound results and likely contribute to the failure
1039 of promising therapeutics when advancing to later stage clinical trials. Fortunately, new
1040 technologies and computational models are now available to solve these problems. Last year, the
1041 FDA Modernization Act 2.0 paved the way for alternative methods to bolster the preclinical data
1042 pipeline, aiming to reduce the dependence on animal models that have frequently resulted in
1043 therapeutic dead ends. The FDA Modernization Act 2.0 reinforced the transitioning beyond
1044 animal models with human cells, organoids, and AI/ML-based approaches (Zushin et al., 2024).
1045 Despite all the advantages that hiPSC-CMs can hold to the discovery and development of anti-
1046 arrhythmic drugs, it is necessary to keep in mind all the current technical, economic and time
1047 limitations that need to be addressed, mainly in terms of electrophysiology. The

1048 electrophysiological maturation state of hiPSC-CMs can determine drugs responsiveness (da
1049 Rocha et al., 2017). As discussed throughout this review, the advent of new and emerging tools
1050 that combine biological systems like stem-cells with cell profiling platforms (multi-omics), new
1051 technologies for data processing, computational modelling, and functional HTS techniques have
1052 made drug discovery and design much more sophisticated and technology-driven. This will
1053 improve the quality, safety, and efficacy of future anti-arrhythmic therapies by enhancing
1054 precision and personalized medicine. In this review we have especially highlighted the promising
1055 therapeutic potential of alternatives like gene therapy and the use of peptide-based therapies in
1056 the treatment of arrhythmias. It is important to note that both technologies are dynamic and
1057 subject to ongoing research and development. As we previously highlighted, gene therapy has
1058 the potential to treat arrhythmias by correcting or compensating for the genetic defects that cause
1059 abnormal heart rhythms, potentially providing a long-term solution. However, limitations include
1060 difficulties in delivering genes safely into heart tissue and ensuring precise and long-lasting
1061 effects without unintended consequences. The other alternative, peptibodies, designed and
1062 engineered to target specific proteins or receptors, offer several potential advantages in treating
1063 arrhythmias like reduced side effects, modularity and customization and biological compatibility
1064 (Chidipi et al., 2022). While peptibodies hold promise in the treatment of various conditions,
1065 including arrhythmias, there are certain limitations and challenges associated with their use.
1066 Those are delivery and stability, immunogenicity, short half-life, development costs, lack of
1067 long-term safety, regulatory approval hurdles, and patient variability. However, ongoing research
1068 and technological advancements may address some of these limitations over time. In summary,
1069 the use of hiPSCs, together with new emerging technologies and computational integration,
1070 offers the unprecedented possibility of improving the discovery of arrhythmia targets,

1071 biomarkers and drugs. New alternatives such as gene therapy and peptide-based therapy open a
1072 new path for the development of a new and promising next-generation antiarrhythmic therapy
1073 with great clinical translation potential.

1074 **Figure Legend**

1075 **Figure 1. Interventional Clinical Trials in the last 10 years.** *A.* Total number of interventional
1076 clinical trial studies in different clinical phases over the last 10 years, extracted from
1077 ClinicalTrials.gov. *B.* Total number of interventional clinical trial studies for arrhythmia
1078 treatment. *C.* Different types of interventions for all clinical trial phases from *B.* *D.*
1079 Pharmacological interventional clinical studies for arrhythmia treatment. AAD, antiarrhythmic
1080 drugs; AF, atrial fibrillation; CPVT, catecholaminergic polymorphic ventricular tachycardia;
1081 LQTS, long QT syndrome; POAF, postoperative atrial fibrillation. PSVT, paroxysmal
1082 supraventricular tachycardia. SGK-1, Serum Glucocorticoid inducible Kinase 1. CaMKII, Ca²⁺
1083 or calmodulin-dependent protein kinase II.

1084 **Data Availability Statement**

1085 The authors declare that all the data supporting the findings of this study are contained within the
1086 paper.

1087

1088 **Author Contributions**

1089 All authors co-wrote the manuscript and conceived the review. G.M.P. performed the analysis of
1090 interventional antiarrhythmic clinical trials and provided writing of iHigh-Throughput Screening,
1091 Drug Repurposing and Advancements in Drug Delivery. P.S.P. wrote hiPSC and OMICS

1092 technology sections. F.M.C. was in charge of writing Computational screening, Peptide-based
1093 treatment, and gene therapy approaches sections. Dr. José Jalife provided writing, supervision,
1094 funding and revision. All authors have read, discussed and agreed to the published version of the
1095 manuscript.

1096 **Conflicts of Interest**

1097 Declare conflicts of interest or state “The authors declare no conflict of interest.”

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2216

2217 **Footnotes**

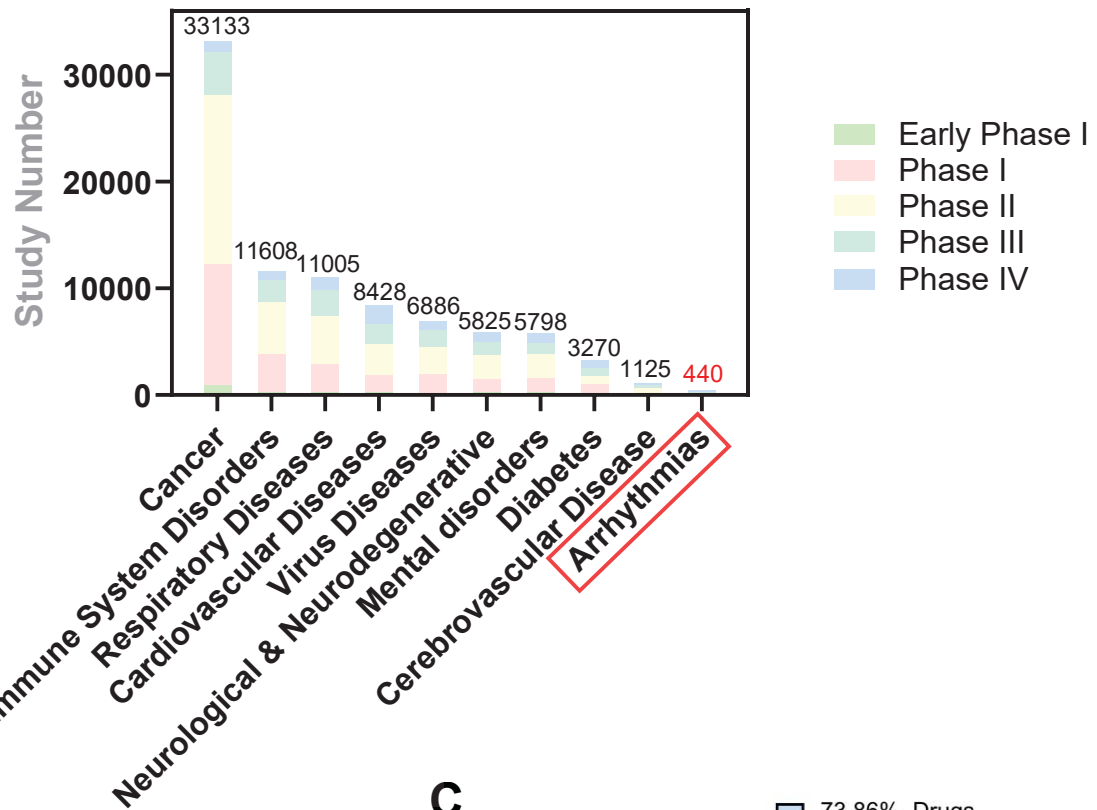
2218 This work was supported by National Institutes of Health R01 HL163943; La Caixa Banking
2219 Foundation [project code638LCF/PR/HR19/52160013]; grant PI20/01220 of the public call
2220 “Proyectos de Investigación en Salud 2020” [PI-FIS-2020] funded by Instituto de Salud Carlos
2221 III (ISCIII); MCIU grant BFU2016-75144-R and PID2020-116935RB-I00, and co-founded by
2222 Fondo Europeo de Desarrollo Regional (FEDER); and Fundación La Marató de TV3642
2223 [736/C/2020]. We also receive support from the European Union's Horizon 2020 Research and
2224 Innovation programme [grant agreement GA-965286]; the Dynamic Microscopy and Imaging
2225 Unit-ICTS-ReDib Grant ICTS-2018-04-CNIC-16 funded by 23 MCIN/AEI
2226 /10.13039/501100011033 and ERDF; project EQC2018-005070-P funded by646 MCIN/AEI
2227 /10.13039/501100011033 and FEDER. CNIC is supported by the Instituto de Salud Carlos III
2228 (ISCIII), the Ministerio de Ciencia e Innovación (MCIN) and the Pro CNIC Foundation, and is a

2229 Severo Ochoa Center of Excellence [grant CEX2020-001041-S649 funded by
2230 MICIN/AEI/10.13039/501100011033].

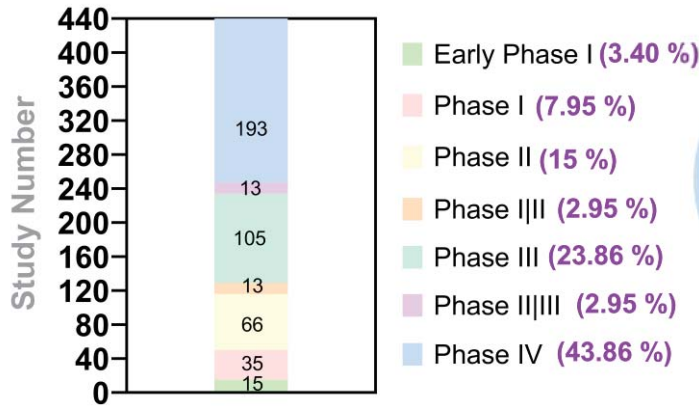
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Interventional Clinical Trial Studies Last 10 Years

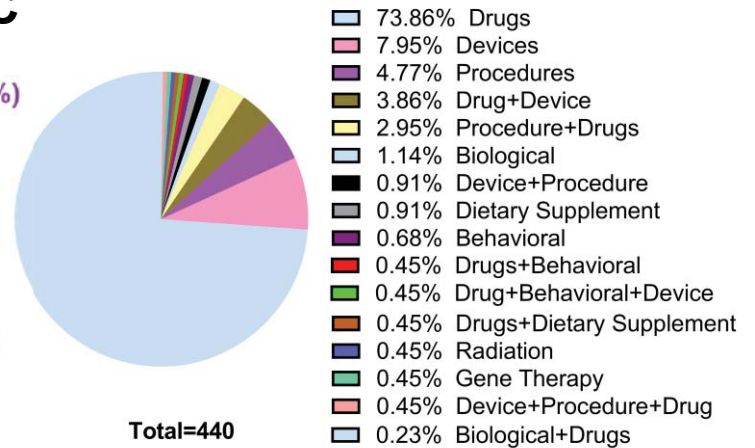
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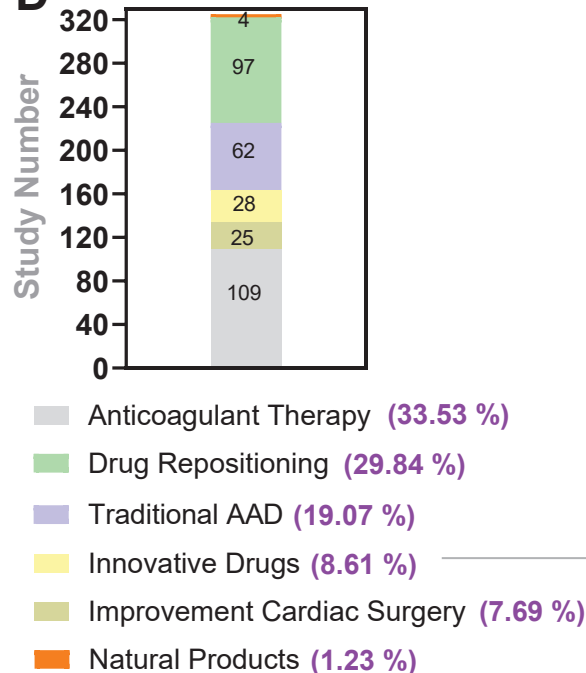
B



C



D



Etripamil (PSVT|AF) (ICaL)
F373280 (AF) (IKur)
BMS-919373 (AF|Paroxysmal AF) (IKur)
Eleclazine (Ventricular Arrhythmia|LQTS|LQTS2-3) (INa)
AP30663 (AF) (IKCa)
S48168 or ARM210 (CPVT1) (RyR channel)
HSY244 (AF) (Undisclosed mechanism)
HBI-3000 (AF) (Multichannel)
GS-6615 (LQTS) (INa,weak IK)
OPC-108459 (AF) (Unknown)
LQT-1213 (LQTS) (SGK-1 inhibitor)
CARDIX-101 (Bradycardia) (Unknown)
CRD-4730 (CPVT1|Heart Defects) (CaMKII inhibitor)
HIP2001 (AF) (Unknown)
OMT-28 (AF) (synthetic analog of epoxyeicosanoids)

Figure 1